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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/630,215	08/01/2000	John F. O'Connor	54205-A-PCT-US/JPW/SHS/MV	7218

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	13

DATE MAILED: 12/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/630,215	O CONNOR ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response, filed 9/26/02 in Paper No. 12 is acknowledged and has been entered. Non-elected claims 44, 46, 49, 51, and 56 have been cancelled. Claims 1-3, 6, 8, 14, 15, 18, 20, 21, 27, 28, 31, 32, 34, 38, 39, 42, and 43 have also been cancelled. Claims 58-68 have been added. Accordingly, claims 58-68 are pending and are under examination.

Rejections Moot

2. Rejections of claims 1-3, 6, 8, 14, 15, 18, 20, 21, 27, 28, 31, 32, 34, 38, 39, 42, and 43 under 35 U.S.C. 112, 102, and 103 are now moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 58-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 58, step a) i) is vague and indefinite in reciting, "recognized by the B152 antibody" because it is unclear what Applicant intends to encompass in reciting,

"recognized". For example, is the B152 antibody specific for the early pregnancy-associated molecular isoform of hCG (EPAMI-hCG), such that it binds EPAMI-hCG.

Claim 58, step a) ii) fails to recite a positive limitation in the claim in reciting, "capable of binding".

Claim 58, step a) iii) is confusing in reciting, "any complex formed between the first and second antibodies and the EPAMI-hCG in the sample" because it is unclear as to whether "any" is meant to encompass "first antibody-EPAMI-hCG complex" or "second antibody-EPAMI-hCG complex" and "first antibody-EPAMI-hCG-second antibody complex" in determining the amount of EPAMI-hCG in the sample, since there does not appear to be any steps of separating "first antibody-EPAMI-hCG complex" and "second antibody-EPAMI-hCG complex" from "first antibody-EPAMI-hCG-second antibody complex", the latter third complex being in a sandwich format. It is therefore, also unclear how measuring of "first antibody-EPAMI-hCG complex" is effected in the absence of a label.

Claim 58, step b) ii) fails to recite a positive limitation in the claim in reciting, "capable of binding".

Claim 59 is vague, indefinite, and lacks clear antecedent support in reciting, "wherein one of the antibodies in each of steps a) and b) is bound to a solid support" because it appears that the first antibody in step a) and the third antibody in step b) should be bound to a solid support (the second antibody in step a) is labeled and the fourth antibody in step b) is labeled); thus, forming a sandwich complexes, but is not clearly and distinctly recited as such.

Claim 62, step i) is vague and indefinite in reciting, "recognized by the B152 antibody" because it is unclear what Applicant intends to encompass in reciting, "recognized". For example, is the B152 antibody specific for the early pregnancy-associated molecular isoform of hCG (EPAMI-hCG), such that it binds EPAMI-hCG.

Claim 62, step ii) fails to recite a positive limitation in the claim in reciting, "capable of binding".

Claim 63, part a) is vague and indefinite in reciting, "recognized by the B152 antibody" because it is unclear what Applicant intends to encompass in reciting, "recognized".

Claim 67 is vague and indefinite in reciting, "recognized by the B152 antibody" because it is unclear what Applicant intends to encompass in reciting, "recognized".

Claim 68 has improper antecedent basis problem in reciting, "The isolated EPAMI-hCG".

Claim 68 is vague and indefinite in reciting, "recognized by the B152 antibody" because it is unclear what Applicant intends to encompass in reciting, "recognized".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 58-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods relying on monoclonal antibody B152 as the antibody which specifically binds to EPAMI-hCG, does not reasonably provide

enablement for any other antibody which binds to EPAMI-hCG. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method of predicting the likelihood of pregnancy outcome in a female subject using an antibody that binds EPAMI-hCG, which is recognized by B152 antibody.

The state of the prior art- the prior art of record fails to disclose a method of predicting the likelihood of a pregnancy outcome in a female subject using an antibody that binds an epitope of hCG comprising the EPAMI-hCG, which is recognized by B152 antibody.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that any antibody, other than the B152 antibody, will work to bind the epitope of hCG characterized as the EPAMI-hCG in a method of predicting the likelihood of a pregnancy outcome in a female subject.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to work for monoclonal antibody B152 which is a monoclonal antibody that is specific for and which specifically binds the epitope of hCG comprising the EPAMI-hCG.

The presence or absence of working examples- there are no working examples that show analogous results for using any antibody that can bind EPAMI-hCG other than B152 antibody.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method of predicting the likelihood of a pregnancy outcome in a female subject using any antibody that binds the epitope of hCG comprising the EPAMI-hCG.

The chemical structure of EPAMI-hCG has not been specifically defined or characterized by the specification. General comments on enhanced potency for signal transduction and increased mono- and tri- antennary content of the branched chain sugars with mostly tetrasaccharide instead of disaccharide are insufficient to establish the nature or structure of the EPAMI-hCG. Monoclonal antibody B152 is the only

disclosed means for identifying what the specification describes as "unexpected and previously uncharacterized" isoform of hCG. MAb B152 was generated against a nicked form of hCG isolated from an undefined choriocarcinoma patient and is not specific for nicked isoforms of hCG (while MAb B151 raised against this same antigen is specific for nicked isoforms of hCG).

Recognition of carbohydrate moieties bound by antibodies is a complex and unpredictable task. Unlike linear amino acid epitopes, which can be readily synthesized in vitro and against which other antibodies can be readily made, carbohydrate epitopes are more complex and difficult to synthesize. Knight (Bio/Techniques, January 1989) likens the task to "wrestling with a cloud". She states that "prediction and control of the expression of oligosaccharide remains elusive and threatens to remain for sometime" and the challenge is "a daunting one." According to Knight, "the structure of carbohydrates is much more complex than that of proteins. Dwek also likens the task of sequencing a carbohydrate to "simultaneously sequencing 40-50 proteins". Because carbohydrate structures are a branching series of linked rings, they can combine in many more ways than can linear peptide chains. For comparison, consider that whole three amino acids can combine in only six ways, "three carbohydrate monomers can form over 1,000 different trisaccharide structures" (see page 39, first column, third and fourth full paragraphs). One skilled in the art would reasonably conclude that, even if one has known that B152 epitope comprised carbohydrate moieties, the synthesis of potential carbohydrate moieties would require undue experimentation.

Even if one skilled in the art were able to identify a region of glycosylated hCG or subunit thereof that bound to a particular antibody, Knight teaches the unpredictability of knowing the exact structure found therein. Knight further states that "on top of this amazing diversity, nature adds what glycobiologists call "microheterogeneity" in the form of discrete subsets- glycoforms- of a glycoprotein. These have different physical and biochemical properties." One skilled in the art would reasonably conclude that these different physical and biochemical properties encompass different epitopes. Knight summarizes that the "demographics of its glycoform populations determine the composite activity of a glycosylated compound. According to Rademacher, Parekh, and Dwek, "any given glycoprotein that consists of different glycoforms will ... have a composite activity, reflecting a weighted average of the activity and incidence of each glycoform" (page 39, third column, second full paragraph). Not only have the glycoforms on hCG not been fully characterized, but neither the glycoisoforms, thereof.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed method for any antibody to bind EPAMI-hCG other than B152 antibody, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work for any antibody other than B152 antibody specific for EPAMI-hCG; 3) there is no proper guidance that shows that any antibody that binds hCG would bind the barely characterized EPAMI-hCG to allow predicting pregnancy outcome in the instant specification, 4) the nature of the invention is a method of predicting the

likelihood of a pregnancy outcome in a female subject using an antibody that binds the EPAMI-hCG, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows generation of a monoclonal antibody that is specific for and specifically binds EPAMI-hCG for use a method of predicting pregnancy outcome in a female subject, 4) the nature of the invention is a method of predicting the likelihood of a pregnancy outcome in a female subject using an antibody that binds EPAMI-hCG, and lastly 7) the claims broadly recite a method of predicting pregnancy outcome in a female subject using any number of antibodies that bind the epitope of hCG comprising the barely characterized EPAMI-hCG.

Given that the nature of B152 epitope was unknown at the time of filing, and the difficulty in making antibodies that recognize on-linear conformational determinants such as carbohydrates, it would require undue experimentation to obtain another antibody which specifically binds to the instant, barely characterized isoform of glycated hCG. Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

5. Claim 68 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The chemical structure of the claimed isolated EPAMI-hCG has not been characterized by the specification nor has the full length sequence of the claimed isolated EPAMI-hCG been fully identified, defined, and disclosed in the specification. General comments on enhanced potency for signal transduction and increased mono- and tri- antennary content of the branched chain sugars with mostly tetrasaccharide instead of disaccharide are insufficient to establish the nature or structure of the EPAMI-hCG. Monoclonal antibody B152 is the only disclosed means for identifying what the specification describes as "unexpected and previously uncharacterized" isoform of hCG. MAb B152 was generated against a nicked form of hCG isolated from an undefined choriocarcinoma patient and is not specific for nicked isoforms of hCG (while MAb B151 raised against this same antigen is specific for nicked isoforms of hCG).

Unlike linear amino acid epitopes, which can be readily synthesized in vitro and against which other antibodies can be readily made, carbohydrate epitopes are more complex and difficult to synthesize. According to Knight, "the structure of carbohydrates is much more complex than that of proteins. Dwek further likens the task of sequencing a carbohydrate to "simultaneously sequencing 40-50 proteins". Because carbohydrate structures are a branching series of linked rings, they can combine in many more ways than can linear peptide chains. One skilled in the art would reasonably conclude that, even if one has known that B152 epitope comprised carbohydrate moieties, the synthesis of potential carbohydrate moieties would require undue experimentation. Knight also teaches the unpredictability of knowing the exact structure found therein as well as "microheterogeneity" in the form of discrete subsets- glycoforms- of a

glycoprotein which have different physical and biochemical properties. According to Rademacher, Parekh, and Dwek, "any given glycoprotein that consists of different glycoforms will ... have a composite activity, reflecting a weighted average of the activity and incidence of each glycoform". One skilled in the art would then reasonably conclude that these different physical and biochemical properties encompass different epitopes. Not only have the glycoforms on hCG not been fully characterized, but neither the glycoisoforms, thereof.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 58-68 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 53, 59, 60, 65, 71, 72, and 77-82 of copending Application No. 09/017, 976, which has been passed to issue for allowance. Although the conflicting claims are not identical, they are not patentably distinct from each other. Specifically, the subject matter claimed in the instant

application is fully disclosed in the referenced patented application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of predicting the likelihood of pregnancy outcome by using an antibody, i.e. B152 antibody, that specifically binds EPAMI-hCG, and quantitating the amount of complex formed therebetween, to determine the amount of EPAMI-hCG isoform, and correlating the result with the amount of INN-hCG in the same sample.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Response to Arguments

7. Applicant's arguments filed 9/26/02 have been fully considered but they are not persuasive.

A) Applicant argues that the specification is enabled for any antibody that binds the analyte, i.e. EPAMI-hCG, because the method is drawn to a modified competitive binding assay in which B152 antibody is labeled. According to Applicant, these antibodies are produced using EPAMI-hCG as immunogen and are screened for their ability to compete with B152 antibody for binding to the EPAMI-hCG epitope recognized by B152 antibody.

In response, the claims, as currently recited, do not appear to recite or be drawn to a modified competitive binding method since the antibodies do not appear to compete for binding to the same EPAMI-hCG epitope as B152 antibody. Additionally, B152 antibody appears to be the only monoclonal antibody identified and defined in the specification as capable of specific binding with the EPAMI-hCG epitope; therefore, the first unlabeled antibody should be a B152 unlabeled antibody that competes for binding with the second labeled B152 antibody.

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 308-9933. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
11/15/02